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(54) Title: MEANS FOR TREATMENT OF DISEASES CAUSED BY MICROORGANISMS WHICH IS A SOLUTION OF SODIUM THIOSULPHATE AND A WEAK ACID AND METHOD OF PREPARING IT

(57) Abstract

The means for treatment of diseases caused by microorganisms represents a mixture of aqueous solutions of sodium thiosulphate and of weak acids in particular ascorbinic. The method for preparing and use of this means for treatment of diseases caused by microorganisms comprises the mixing of its components under sterile conditions and at ambient temperature whereby in case of intravenal administering, it is effected as preferred embodiment in a syringe by consecutive aspiration of the components and for local administering in a suitable vessel. The means represents a mixtures of two components whereby in the organism are introduced beside the non-reacted excess of sodium thiosulphate and the obtained by the mixing sodium salt of the acid, sulphur and $NaHSO_3$. Their preparation and insertion in the organism provides for a rational and original way of introducing these substances as well as a complete interaction with internal processes in the organism in order to achieve a vigourous therapeutic effect. The tests which have been performed show that the means has a wide range of action against disease causing microorganisms while being practically harmless.

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phate in the mixture with regard to the amount of weak acid is equal or more than the amount of sodium thiosulphate according to the respective stoichometric equation that is sufficient for complete reacting between both components. When the quantity of sodium thiosulphate is considerably more than the needed for the reaction it is established a significant excess of it in the obtained mixture.

According to a prefered embodiment in the means for treatment of diseases caused by microorganisms is used as a weak acid ascorbinic acid $C_6H_8O_6$ , whereby the ratio of amount of sodium thiosulphate $Na_2S_2O_3.5H_2O$ to the amount of ascorbinic acid $C_6H_8O_6$ is not less than 1 : 0.7. Sodium Thiosulphate in the mixture can be with or without 5 molecules $H_2O$. A wide range of therapeutic effect is shown by the means in which the ratio of the amount of sodium thiosulphate $Na_2S_2O_3.5H_2O$ to the amount of ascorbinic acid $C_6H_8O_6$ is 4:1.

The method for preparation and use of the means for treatment of diseases caused by microorganisms consists in that its components - aqueous solutions of sodium thiosulphate and of weak acids are mixed at ambient temperature and sterile conditions until are obtained the sodium salt of the acid, sulphur and $NaHSO_3$ immediately before administering it externally or intravenally.

Usually the mixing of both components is effected in a syringe by consecutive inserting of aqueous solutions of sodium thiosulphate and of weak acids or mixing of solutions of them before the needle in case where are used systems. The basic requirement for injecting immediately after obtaining the mixture should be observed strictly since if the obtained mixture is retained a longer time sulphur particles are increasing which results in a decrease of efficiency and eventually it can conduct to unwanted results. In order to avoid it it is purposeful to use technical means for fixing

the period of mixing and to employ syringes with filters.

In the multiple experiments following the rule according to the proposed method the mixture to be inserted in the blood without retaining immediately after its preparing there have not been observed any harmful after-effects so that the means is practically innocuous in the administered therapeutic dose.

According to the method in the reaction proceeding between the aqueous solutions of sodium thiosulphate and weak acids in particular ascorbinic acid which is prefered and is satisfying all requirements is obtained sodium salt of ascorbinic acid, sulphur and $NaHSO_3$. In the blood besides these three substances are entering and considerable amounts of sodium thiosulphate since it is prefered its quantity to be in excess of the required for the complete running of the reaction in mixing both components.

The experiments show also that a mixture of four parts 10%-aqueous solution of sodium thiosulphate and one part 10%-aqueous solution of ascorbining acid has a very high therapeutic effect and a wide range of action.

The means for treatment of diseases caused by microorganisms and the method for its preparation and use achieve in a rational and original way the problem of introducing sodium salt of ascorbinic acid, colloidic sulphur and sodium bisulphite as well of sodium thiosulphate in excess into the blood with therapeutic purpose without bringing harmful after-effects.

The proposed means and method for its preparation and use are elucidated more in detail by following examples:

A. Test for harmfulness. A mixture of four parts of 10%-aq. solution of sodium thiosulphate and one part of 10%- aq. solution of ascorbinic acid prepared at ambient temperature and sterile conditions is used immediately after mixing usually

within a three minute period.

1. Tests for determining of LD-50. By means of multiple serial experiments of mice with intravenal insertion of the preparation it has been determined that the dose LD-50 is between 1.28 and 1.76 g per kg of alive weight.

2. Tests for sharp tolerance of rabbits. In intravenal administering of a dose of 200 mg per 1 kg alive weight it has been established that there are no damages.

3. Tests with white rats for determining the influence of the preparation on blood pressure, cardiac frequence, frequence of breathing in intravenal administering of three different doses: 50 mg, 100 mg and 200 mg per kg alive weight. Only in the case of inserting 200 mg for kg alive weight it was observed a slight acceleration of breathing during half to one minute only in the moment of injecting being transitional. With the other doses there were no changes.

4. Tests with dogs , race "Beagle" with weight 10 to 15 kg. Each day were administered at once doses of 50 mg and 100 mg per kg alive weight during 30 days. Testing was carried out on the $7^{th}$ day and on the $48^{th}$ hour of the $30^{th}$ day after administering. Following results were obtained: haematological data - no deviations from standard blood analysis and blood curdling. Biochemical data: there are no changes in alkaline - equilibrium and in results from proteinic, carbohydratic and lipidic exchange and in electrolyte contents(sodium, potassium, phosphor, fluorides). There are also no data for modifications in liver and kidney function.

<u>B. Test for treatment of diseases by local administering</u>.

A mixture is used consisting of four parts of 10%-aqueous solution of sodium thiosulphate and one part of 10%-aq. solution of ascorbinic acid( in the second case with citric acid) which was prepared in mixing at ambient temperature .

and under sterile conditions. It is administered immediately in the period from 3 to 5 min. The following experiments have been carried out directly after mixing:

1. For keratite from human herpes virus type I on rabbits with clearly expressed viral damages. With drops in the eyes was achieved a complete healing.
2. Treatment of chronic endometrites of cows with an aqueous solution of $Na_2S_2O_3 .5 H_2O$ and citric acid. Complete healing
3. Treatment of chlamidiose of human beings - all healed.
4. Treatment of herpetic keratite and zoster ophtalmica in human beings. Treatment of eye damages - all healed.

C. Tests for treatment by intravenal administering. Of great practical and theoretical interest are the tests carried out by intravenal administering of a mixture comprising four parts of 10%- aqueous solution of sodium thiosulphate and one part of 10% aqueous solution of ascorbinic acid. Mixing is performed at ambient temperature and under sterile conditions and it is administered immediately in the interval of 30 to 40 s. The therapeutic dose used is of 40 mg per kg alive weight while the sodium thiosulphate is 32 mg and ascorbinic acid-8 mg. Tests have been performed immediately after mixing. Data show that the chemiotherapeutic index -Dosis tolerantia to Dosis Curatica is very favourable.

$\frac{DT}{DC} > 30$ Following tests were carried out:

1. Tests with rabbits, infected by beef herpes virus type I. All treated rabbits have been healed.
2. Treatment of calves suffering from gastroenterite(colibacteriose) with a mixed infection. 83% habe been healed. It is stated that the died calves were treated too late.
3. Treatment of rams suffering from Brucella ov. by three- and five-time injecting. Complete healing has been achieved.
4. Treatment of mice malaria. After one to two-time treatment it is observed a considerable prologation of mice life with evident decrease in index of erythrocytic parasitizing. The experiment has been discontinued.

6. Treatment of sick persons suffering from AIDS. and carriers of virus HIV. Good clinical results have been attained as well as temporary disappearing of HIV from the blood.However the therapeutic treatments have not yet been terminated and no definite results are available at present.

# C L A I M S

1. Means for treatment of diseases caused by microorganisms, characterized in that it represents a mixture of aqueous solutions of sodium thiosulphate and of weak acids in particular organic acids which during the process of reaction with sodium thiosulphate are forming sodium salt of the acid, sulphur and $NaHSO_3$ whereby the amount of sodium thiosulphate with respect to the amount of weak acids is equal or larger than the amount determined according to the respective stochiometric equation.

2. Means for treatment of diseases caused by microorganisms according to claim 1, characterized in that as weak acid is used ascorbinic acid $C_6H_8O_6$ whereby the ratio of amount of sodium thiosulphate $Na_2S_2O_3$;5 $H_2O$ to amount of ascorbinic acid $C_6H_8O_6$ is not less than 1 : 0.7.

3. Means for treatment of diseases caused by microorganisms according to claims 1 and 2, characterized in that it represents a mixture consisting of four parts of 10%-aqueous solution of sodium thiosulphate $Na_2S_2O_3$. 5 $H_2O$ and one part of 10%- aqueous solution of ascorbinic acid $C_6H_8O_6$.

4. Method for preparing and use of this means for treatment of diseases caused by microorganisms according to claims 1, 2, 3, characterized in that the aqueous solutions of sodium thiosulphate and of the weak acids are mixed until are obtained the sodium salt of the acids, sulphur and $NaHSO_3$ at ambient temperature and under sterile conditions immediately before administering the mixture externally or intravenally.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/BG 91/00001

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 33/04

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| IPC5 | A 61 K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category * | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | Dialog Information Services, File 351, World Patent Index 81-91, Dialog accession no. 007066043, Ishimoto T: "Antimycotic agent without irritant effect or strong smell contg. thiophosphate,alum and acid", DE 3629385, A, 870305, 8710 (Basic) -- | 1-4 |
| X | Dialog Information Services, File 351, World Patent Index 81-91, Dialog accession no. 007315007, Kaza Vaskhnil veter: "Salt solution veterinary treat calf; contain supplementary salt ascorbic acid increase therapeutic efficiency", SU 1246448, A, 870223, 8744 (Basic) -- | 1-4 |
| X | US, A, 4474759 (VOJISLAV PETROVICH) 2 October 1984, see column 2, line 1 - line 46 -- | 1-4 |

* Special categories of cited documents:[10]

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## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 13th December 1991 | 27. 01. 92 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | Nuria TORIBIO |

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 4 (partly), because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

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[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/BG 91/00001

SA 49333

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/10/91
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| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| US-A- 4474759 | 02/10/84 | US-A- | 4469678 | 04/09/84 |
| DE-A1- 2445679 | 27/03/75 | FR-A-B- | 2269960 | 05/12/75 |
| | | US-A- | 4148885 | 10/04/79 |
| US-A- 4929378 | 29/05/90 | AU-B- | 602150 | 04/10/90 |
| | | AU-D- | 7494287 | 07/01/88 |
| | | DE-A- | 3721545 | 07/01/88 |
| | | FR-A- | 2600887 | 08/01/88 |
| | | JP-A- | 63146811 | 18/06/88 |

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

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